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Support for mid-life anxiety diagnosis as an independent risk factor for dementia: a systematic review.

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3 **Support for mid-life anxiety diagnosis as an independent risk factor for**
4 **dementia: a systematic review.**
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Abstract

Objectives: Anxiety is an increasingly recognised predictor of cognitive deterioration in older adults and those with mild cognitive impairment (MCI). Often believed to be a prodromal feature of neurodegenerative disease, anxiety in mid-life and older age may potentially act as an independent risk factor for dementia.

Design: A systematic review of the literature on anxiety diagnosis and long-term risk for dementia was performed following published guidelines.

Setting and participants: Electronic databases were searched for peer-reviewed journals up until 8 March 2017. Publications reporting hazard/odds ratios for all-cause dementia based on clinical criteria from prospective cohort or case-control studies were selected. Included studies measured clinically significant anxiety in isolation or after controlling for symptoms of depression, and reported a mean interval between anxiety assessment and dementia diagnosis of at least 10 years. Methodological quality assessments were performed using the Newcastle-Ottawa scale.

Outcome measure: HR/ORs for all cause dementia.

Results Searches yielded 3510 articles, of which four (0.02%) were eligible. The studies had a combined sample size of 29,819, and all studies found a positive association between clinically significant anxiety and future dementia. Due to the heterogeneity between studies, a meta-analysis was not conducted.

Conclusions Clinically significant anxiety in mid-life was associated with an increased risk of dementia over an interval of at least 10 years. These findings indicate that anxiety may be a risk factor for late-life dementia. With increasing focus on identifying modifiable risk factors

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3 for dementia, more high quality prospective studies are required to clarify whether clinical
4
5 anxiety is a risk factor for dementia, separate from a prodromal symptom.
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8 **Strengths and limitations of this study:**

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- 10
11 • This systematic review used a rigorous methodology, with broad search terms and
12 precisely pre-defined inclusion and exclusion criteria to investigate a life-course
13 association between a potentially modifiable risk factor, anxiety, and dementia.
14
- 15
16 • Strict exclusion criteria were used to remove studies that did not either discuss
17 anxiety diagnosis alone or control for depression, to account for high levels of
18 anxiety-depression comorbidity
19
- 20
21 • Study quality was formally investigated using the Newcastle-Ottawa scale
22
- 23
24 • The review was limited by the lack of assessment of cognition at baseline in
25 retrospective studies, however, the length of look-back, minimises the likelihood of
26 cognitive impairment at baseline
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- 28
29 • The small number and heterogeneity of study designs rendered a meta-analysis
30 inappropriate, therefore formal statistical analyses could not be performed
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41 **Introduction**

42
43 Dementia, and more specifically Alzheimer's disease (AD), is a progressive neurocognitive
44 disease. In the absence of any disease modifying treatments, there is increasing focus on
45 primary prevention to reduce risk of its development, and on early intervention to
46 potentially slow the progression of dementia. A better understanding of risk factors for
47 dementia is therefore vital for improving therapeutic interventions. Alongside a number of
48 well described cardiovascular risk factors [1] increasing evidence has highlighted the
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3 association between psychiatric illnesses and the development of late-onset dementia
4
5 (Marchant & Howard, 2015). Further work is needed to understand whether these
6
7 psychiatric symptoms and illnesses represent prodromal symptoms or act as independent
8
9 risk factors. Depression has been consistently related to the development of dementia [2].
10
11 Three meta-analyses have reported that a diagnosis of depression is associated with up to a
12
13 twofold increase in risk for dementia [2–4]. Ownby and colleagues further report that a
14
15 longer interval between diagnosis of depression and diagnosis of dementia is significantly
16
17 associated with an increased odds ratio (OR) of developing dementia. This substantiates
18
19 interpretations of depression as a risk factor for developing dementia, whereas a stronger
20
21 association over shorter intervals would have been more indicative of prodromal symptoms
22
23 [2], however a recent study opposes this [5].
24
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27

28
29 Although anxiety is a prevalent psychiatric disorder [6] and commonly co-occurs with
30
31 depression, the impact of anxiety on risk for cognitive decline and dementia has been far
32
33 less studied. Anxiety symptoms are commonly experienced in the years preceding a
34
35 dementia diagnosis [7], and have been associated with cognitive decline and the
36
37 progression from MCI to AD [8–10]. A recent review reported that anxiety and
38
39 neuropsychiatric symptoms not reaching clinically diagnostic levels were associated with
40
41 increased risk of dementia [11]. The authors indicated that anxiety was likely a prodromal
42
43 symptom of dementia in these community samples. This may well have been the case,
44
45 particularly given the relatively short intervals between assessment of anxiety symptoms
46
47 and assessment of dementia, however, this does not preclude anxiety also being a risk
48
49 factor. This could more easily be investigated with longer intervals between anxiety
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51 assessment and dementia diagnosis, as the studies that have investigated this association
52
53 within a 5-10 year interval have reported variable results [12,13].
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3 The average length of prodromal preclinical cognitive decline has been proposed to be
4
5 between 5-6 years [14], and individuals diagnosed with MCI may progress to AD within 5
6
7 years [15]. Therefore, examining studies with at least a 10-year interval between anxiety
8
9 assessment and dementia diagnosis would increase likelihood that anxiety is independent
10
11 from the dementia prodrome.
12
13

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15 It is possible that anxiety symptoms meeting diagnostic threshold will have a stronger
16
17 association with dementia than general symptoms because this has been shown with
18
19 depression [3]. To date, there has been no systematic review to investigate the association
20
21 between clinically significant anxiety and dementia. The aim of this study was therefore to
22
23 review the literature examining the association between clinically significant levels of
24
25 anxiety and dementia risk over a longer timescale (>10 years).
26
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28 29 **Methods**

30
31 This systematic review followed the Preferred Reporting Items for Systematic Reviews and
32
33 Meta-analyses (PRISMA) and Centre for Reviews and Dissemination (CRD) guidance for
34
35 undertaking reviews in health care [16].
36
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38 39 *Search strategy*

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41 A systematic literature search of MEDLINE, PSYCINFO and EMBASE databases was
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43 conducted of articles published up until 8th March 2017 to identify articles reporting
44
45 analyses of the association between anxiety (as defined by clinical diagnosis or self-report
46
47 scales with a clinically significant threshold) and dementia or MCI incidence. Search terms
48
49 used consisted of: (dement* OR Alzheimer* OR "mild cognitive impairment" OR MCI) AND
50
51 (anx* OR "generalised anxiety disorder" OR GAD) AND (risk* OR odds). We aimed to identify
52
53 articles discussing (1) diagnosis of any type of dementia or MCI, (2) anxiety diagnosis, and
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3 (3) risk of dementia. The search was restricted to human studies and those published in
4
5 English. Reference lists were searched for additional relevant articles. Searches were
6
7 conducted by a single reviewer (AG). An independent review of all screened articles was
8
9 conducted by a second reviewer (MS). Any disagreement was resolved by consensus with a
10
11 third reviewer (NM).
12
13

14 15 *Selection Criteria and Article Screening*

16
17 Inclusion criteria were 1) a diagnosis of anxiety or an assessment of anxiety symptoms
18
19 meeting diagnostic criteria using a standardised assessment tool, excluding populations with
20
21 post-traumatic stress disorder (PTSD) or obsessive-compulsive disorder (OCD); 2)
22
23 population-based studies where anxiety is assessed at least – on average – 10 years
24
25 preceding final clinical assessment for dementia in line with previous meta-analyses on
26
27 depression using intervals of at least 10 years [2]; 3) a diagnosis of dementia using validated
28
29 criteria (e.g. Diagnostic Statistical Manual III-IV (DSM III-IV), International Classification of
30
31 Diseases 10 (ICD-10)); 4) late-onset dementia diagnoses (aged ≥ 65 years). Eligible articles
32
33 were identified by performing an initial screen of titles and abstracts, followed by a full
34
35 article review of those that passed screening. All retrospective and prospective studies that
36
37 met these criteria were selected.
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43 *Data extraction*

44
45 Outcome measures related to anxiety and dementia diagnosis were independently
46
47 extracted by two authors (AG, MS). Disagreements were resolved through discussion. Study
48
49 design, sample characteristics (including educational level and age), follow-up length,
50
51 dropout rate, anxiety (including measure and baseline score where appropriate), criteria for
52
53 assessing dementia, and measurements of depression as a confounder (including measure
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3 and baseline score), were recorded. In cases of insufficient data, authors were contacted by
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5 email.

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8 INSERT FIGURE 1
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10 *Study Quality*

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12 Two authors (AG, MS) independently assessed study quality and risk of bias using the
13
14 Newcastle-Ottawa scale, which contains separate quality assessment instruments for case-
15
16 control and cohort studies.
17
18

19 **Results**

20 *Literature Search*

21
22 The literature search detected 3509 citations, of which two were duplicates. One further
23
24 paper was identified manually during reference screening. After screening titles and
25
26 abstracts, 18 full-text articles were assessed for eligibility. Fourteen articles were excluded
27
28 based on criteria described earlier (Figure 1), four studies were included in the final review.
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34 *Study Characteristics*

35
36 Characteristics of the four selected studies are shown in Table 1. Clinically significant anxiety
37
38 was documented based on clinical diagnosis using International Classification of Diseases 10
39
40 (ICD-10) criteria (n = 2), the State Trait Anxiety Inventory (STAI, n = 1) and a subscale of the
41
42 State Trait Personality Inventory (STPI, n = 1).
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46
47 Gallacher et al. (2009) measured anxiety using the STAI, which has a range from 20 to 80
48
49 [17]. This questionnaire is arguably the gold standard for assessing anxiety symptoms. A
50
51 clinically significant cut-off of 39-40 has been proposed [18,19]. Gallacher et al. (2009)
52
53 categorised 'high anxiety' as having a STAI score between 35 and 72, compared to a 'low
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3 anxiety' group who had a STAI score between 20 and 34. Boot et al. (2013) and Zilkens et al.
4
5 (2014) used ICD-10 criteria to diagnose an anxiety disorder.
6

7
8 Petkus et al. (2016) assessed anxiety using state anxiety subscale of the State-Trait
9
10 Personality Inventory (STPI), which contains a subset of items from the STAI. Participants
11
12 scoring at least one standard deviation above the population mean, equating to a score of
13
14 ≥ 25 out of 40, were categorised having 'high anxiety'. This cut-off indicated clinically
15
16 significant anxiety, therefore rendering the study suitable for inclusion in this review.
17
18

19
20 Dementia diagnosis was in most cases assessed using DSM III-IV (n = 2) or ICD-10 criteria (n
21
22 = 1), although the study by Boot et al. (2013) assessed Dementia with Lewy Bodies (DLB) by
23
24 clinical diagnosis using published criteria [20].
25

26
27 Sample sizes of the studies ranged from 441 to 27 136 participants, recruited from both or
28
29 either community and hospital inpatient/outpatient populations. Gallacher et al. (2009) and
30
31 Petkus et al. (2016) conducted prospective cohort studies using community populations that
32
33 excluded dementia at baseline. Zilkens et al. (2014), and Boot et al. (2013) conducted
34
35 matched case-control studies, which analysed community and hospital records for anxiety
36
37 diagnosis and therefore did not include a cognitive assessment at baseline to exclude
38
39 dementia. The proportion of females in each study ranged from 0 to 56.6%. Educational
40
41 level was recorded for all but one study; which ranged from 55% with no qualifications to
42
43 95% with >9 years of education.
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49 INSERT TABLE 1
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51 *Anxiety diagnosis association with dementia*

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53 All studies included in this review found a significant increase in the number of dementia
54
55 diagnoses in patients who had a clinical anxiety diagnosis or experienced clinically significant
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3 anxiety symptoms on average at least 10 years prior to their diagnosis of dementia; Zilkens
4
5 et al. (2014): OR = 1.61 (95% CI 1.28-2.02), Boot et al. (2013): OR = 7.4 (95% CI 3.5-16),
6
7 Gallacher et al. (2009): OR = 1.62 (95% CI 0.59-4.41) and Petkus et al. (2016): OR = 1.48 (95%
8
9 CI 1.01-2.18), respectively.
10

11
12 Each study controlled for a range of demographic factors, with all controlling for vascular
13
14 and other psychiatric risk factors (Table 2 and 3). All studies assessed and controlled for
15
16 depression symptoms in their analysis. Boot et al. (2013) found a stronger association
17
18 between anxiety diagnosis alone with future dementia than either depression diagnosis
19
20 alone or mixed anxiety and depression diagnosis, although the number of individuals with
21
22 anxiety was markedly larger than those in the other two categories (anxiety alone n=168;
23
24 depression alone n=52; anxiety and depression n=56). Although Zilkens et al. (2014)
25
26 assessed a range of psychiatric diagnoses including anxiety and depression, they did not
27
28 assess their interaction. Petkus et al. (2016) and Gallacher et al. (2009), whilst controlling for
29
30 depression, made no assessment of the comparative strength of relationship or their
31
32 interaction.
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38 *Study Quality Rating*

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40 All studies included were rated highly on the Newcastle-Ottawa scale [21]. From a maximum
41
42 score of 9, Boot et al (2013) was rated 8; and Zilkens et al. (2014), Petkus et al. (2016) and
43
44 Gallacher et al. (2009) were each rated 7. These studies were of similar quality to those
45
46 included in a recent meta-analysis examining dementia risk estimates associated with late-
47
48 life depression [3].
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52 Three of the studies had representative samples of community populations; the fourth led
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54 by Gallacher et al. (2009) included only men. All controlled for a range of both demographic,
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3 physical and psychological health factors. All outcomes were assessed either via secure
4 health records, or independent validation. Gallacher et al. (2009) experienced 20% loss to
5 follow-up, which compares favourably to the pre-mentioned Cherbuin et al. (2015) review
6 which considered studies with an attrition rate of between 4.3% and 55.46%, and a review
7 of MCI drug studies with attrition rates varying from 12% to 49% [22]. Petkus et al. (2016)
8 did not clearly report loss to follow-up. For both case-control studies, the primary care
9 records did not include a cognitive assessment at baseline. Therefore, pre-existing cognitive
10 impairment before diagnosis cannot be ruled out, although long look-back periods make this
11 less likely.
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24 INSERT TABLE 2

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27 INSERT TABLE 3

28 29 30 **Discussion**

31
32 We systematically reviewed evidence for a relationship between clinically significant anxiety
33 and risk of late-onset dementia over a mean interval of at least 10 years from anxiety
34 assessment to dementia diagnosis. Four studies met inclusion criteria, and each were of
35 high quality. All studies found an association between clinically significant anxiety and
36 increased likelihood of a dementia diagnosis, even after accounting for potential
37 confounders (including depression symptoms).
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46 Anxiety symptomatology has previously been related to dementia risk and cognitive decline,
47 although not conclusively [9,23]. A recent systematic review reported a positive association
48 between anxiety symptoms and dementia diagnosis over a short time interval [11]. Further,
49 the association was stronger with smaller intervals between assessment of anxiety and
50 dementia diagnosis. As a result, the authors concluded that anxiety may result from a
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3 prodromal state of dementia, where an increase in anxiety may be due to an individual's
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5 insight into their early, subjective experience of cognitive decline [11]. Given the short time
6
7 interval between assessments, Gulpers et al. were unable to determine whether anxiety
8
9 could also serve as an independent risk for dementia. This review reports solely articles that
10
11 were not included Gulpers et al.'s analyses, and therefore furthers their work by providing
12
13 an independent assessment of the anxiety-dementia association.
14
15

16
17 The prodromal phase of dementia can begin several years before objective dementia is
18
19 manifest. In the present review, we sought to minimise the potential influence of pre-
20
21 clinical cognitive decline by including only studies that assessed anxiety and dementia
22
23 diagnoses over an extended period. Three studies (Zilkens et al. 2014; Gallacher et al. 2009;
24
25 Petkus et al. 2016) demonstrated a mean interval of at least 10 years between the anxiety
26
27 and dementia evaluations. Boot et al. (2013) analysed participant's lifelong medical record,
28
29 however, the mean interval between anxiety and dementia diagnosis was not reported. The
30
31 results summarised here suggest that anxiety may also be an independent risk for dementia.
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36 Findings from this review corroborate recent evidence that anxiety symptoms or diagnosis
37
38 are associated with risk of MCI [28,29]. These findings further complement the association
39
40 between depression and dementia diagnosis [3], which is particularly relevant due to high
41
42 levels of anxiety-depression comorbidity. Moreover, they lend support for the proposal that
43
44 multiple psychiatric risk factors are implicated together as a latent risk factor for dementia
45
46 [30].
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49
50 It has recently been suggested that a longer interval period between anxiety and dementia
51
52 diagnosis may provide evidence for a common biological pathway linking anxiety,
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54 depression, and dementia [26]. An abnormal stress response, such as exhibited in anxiety
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3 disorders, may be associated with accelerated cellular ageing and neuro-progression (a
4
5 pathological reorganisation of the central nervous system) resulting in increased
6
7 neurodegeneration, neuronal apoptosis and lowered neuroplasticity [31]. Although
8
9 glucocorticoid, inflammatory mediator and vascular disease mechanisms are hypothesised
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11 [2,32], as yet, no convincing candidate biological mechanism linking anxiety and cognitive
12
13 impairment exists.
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15

16
17 The results of this review should be interpreted in the light of their limitations. Only studies
18
19 that had been published and written in English were included, which may limit extrapolation
20
21 across broader populations. Retrospective studies did not examine baseline cognition and
22
23 therefore cannot exclude early cognitive decline at the time of anxiety assessment,
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25 however, the length of look-back, ranging from over 10 years to the first entry of an
26
27 individual's medical record, minimises the likelihood of cognitive impairment at baseline. To
28
29 account for high levels of anxiety-depression comorbidity, this review included only papers
30
31 discussing anxiety diagnosis alone, or those that controlled for depression symptomatology.
32
33 However, the Zilkens et al. (2014) and Boot et al. (2013) cannot completely exclude overlap
34
35 of these two commonly comorbid illnesses because their occurrence was ascertained from
36
37 lists of diagnoses in medical records. Furthermore, results must be interpreted in the light of
38
39 proposals that the prodromal AD pathophysiologic processes may develop beyond 10 years
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41 before the onset of clinical symptoms [33].
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47 Whether reducing anxiety in middle-age would result in reduced risk of dementia remains
48
49 an open question. The effect of treatment of anxiety using pharmacologic and non-
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51 pharmacologic therapies during midlife on later risk for dementia has not yet been
52
53 investigated. Benzodiazepines, commonly used in the treatment of anxiety, have been
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3 shown to increase risk of mortality in some groups [34]. It is possible that diverse non-
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5 pharmacological therapies, including talking therapies [35] and mindfulness-based
6
7 interventions and meditation practices [36], that are known to reduce anxiety in midlife,
8
9 could have a risk-reducing effect, although this is yet to be thoroughly researched.
10

11
12 Given the high prevalence of anxiety seen in primary care, we suggest that general
13
14 practitioners could consider anxiety alongside depression as an indicator of risk factor for
15
16 dementia. To improve the rate of earlier diagnosis of dementia, close monitoring of subtle
17
18 cognitive decline in older adults with a history of anxiety, depression and cerebrovascular
19
20 disease would be encouraged. This review expands our understanding of anxiety as a
21
22 potentially modifiable risk for dementia. Given the limited number of studies investigating
23
24 the anxiety-dementia relationship, further research is required to assess underlying
25
26 mechanisms that link these disorders, and to disambiguate anxiety's potential role as a risk
27
28 factor as separate from a prodromal symptom of dementia.
29
30
31

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51 **Contributors**

1
2
3 AG contributed to design of the study, data screening and extraction, drafting of the
4
5 manuscript and submission. MS contributed to literature search, data screening and
6
7 extraction, and manuscript preparation. JDH contributed to the study design, provided
8
9 methodological expertise and editing of the manuscript. NLM contributed to the
10
11 conception and study design, data interpretation, and editing of the manuscript.
12
13

14 15 **Competing interests**

16
17
18 None of the contributing authors have any conflicting interests to declare.
19
20

21 22 **Data sharing statement**

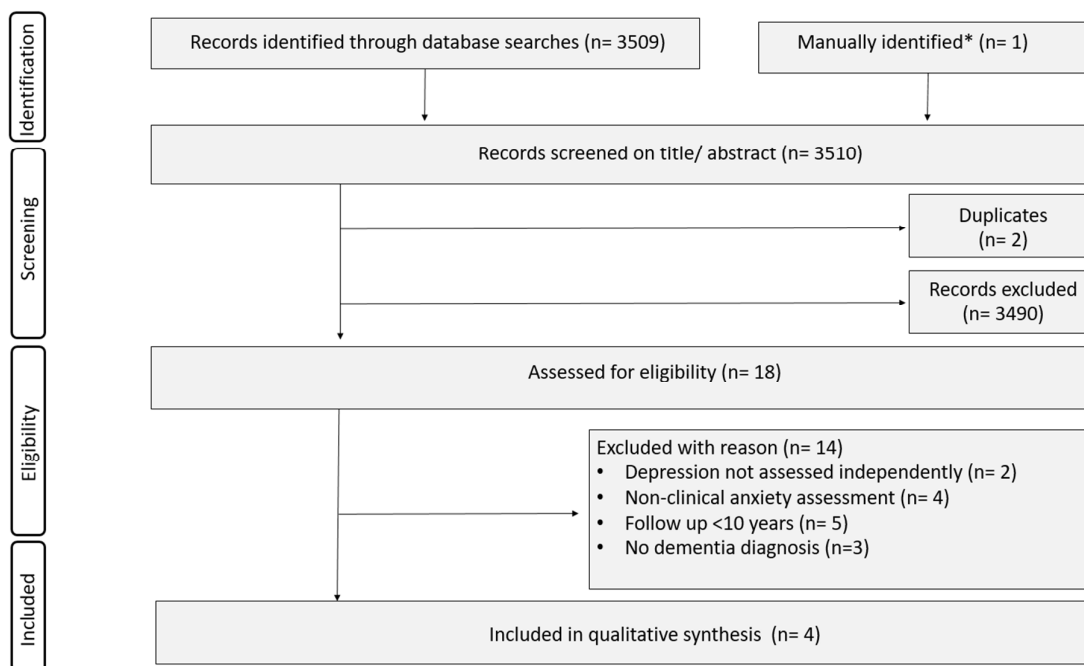
23
24
25 No additional data are available.
26
27

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27 **Figure 1** Flowchart of the search and study selection process; * = manually identified from Petkus et
 28 al. (2016)

Table 1 Study Characteristics

	Study type and setting; location	Follow-up/ Look back period; years (SD)	Mean age years (SD)	Female n (%)	Education level; no. (%)	Drop-out rate/Non-response rate %	Baseline cognition measure	Anxiety measure; cut-off	Baseline anxiety, %	Controls for depression; baseline depression measure	Dementia diagnosis; criteria (no. cases); OR/HR (95% CI)
Boot et al. 2013 (n=441)	Population based matched case-controlled, Mayo Clinic Rochester, Minnesota, USA	Lifelong diagnoses documented by medical record	72.5 (7.3) – DLB cases age at diagnosis	103 (23.1)	>9 yrs education; (95)	NR	NR	Clinical diagnosis, present in medical history section of medical record	23, 27% cases; 14, 5% controls	Yes; clinical diagnosis from medical history record	DLB diagnosis by behavioural neurologist; published criteria by McKeith et al (2005) (n=147); OR 7.4 (3.5-16)
Gallacher et al. 2009 (n=1160)	Prospective, community based cohort; Caerphilly, Wales, UK	Mean follow up period; 17.3 (1.3)	56.1 (4.4) – mean age at inclusion	0	no qualifications; 601 (55)	20	NR; dementia unlikely at inclusion (mean age <60 yrs)	STAI; score of ≥35	585, 50%	Yes; GHQ-30	Dementia diagnosis; DSM-IV or medical records (n=90); OR 1.62 (0.59-4.41)
Petkus et al. 2016 (n=1082)	Prospective, community based cohort; Swedish twins drawn from Swedish Twin Registry, Sweden	Follow up period; 28 (0)	60.86 (11.15) – mean age at inclusion	612 (56.6)	Beyond elementary education; 423 (39)	29.8	MMSE	State anxiety subscale of STPI; STPI > 1 SD Q1-Q4 (assessments over 4 time-points)	403, 37%	Yes; OARS depression subscale, CES-D	Dementia diagnosis; DSM-III or DMS-IV (n=172); HR 1.48 (1.01-2.18)
Zilkens et al. 2014 (n=27136)	Population based matched case-controlled, Western Australia	Mean look back period; cases 20.4 (10.4), controls 20.0 (10.3)	78.7 (4.7) – mean age at final time point	15359 (56.6)	NR	6.17 (excluded individuals)	NR	Clinical diagnosis using ICD-10 AM (Australian Modification) codes documented in health records; meeting diagnostic threshold	379, 2.8% cases	Yes; clinical diagnosis by GP	Dementia diagnosis; ICD-10 (n=13568); OR 1.61 (1.28-2.02) (>10 years look back period)

(CES-D = Centre of Epidemiological Studies depression subscale, DLB = Dementia with Lewy bodies, GHQ-30 = 30-item general health questionnaire, NR = not recorded; OARS = older American resources and services; STAI = State trait anxiety inventory; STPI = State trait personality inventory)

Table 2 Case controlled studies: Newcastle-Ottawa scale for assessment of quality of included case controlled studies (+ / - represents whether individual criterion within the subsection was fulfilled)

	Acceptable Criteria	Zilkens et al. 2014		Boot et al. 2013	
Selection					
Case definition	With independent validation	Record linkage from Western Australian Data Linkage System and Death Registry, no independent validation	-	Assessment for DLB using behavioural neurologist	+
Representativeness of cases	Consecutive or representative series of cases	All dementia cases in period 2000-2009 identified via read-code; lower limit index dementia age 65 years, upper limit 84 years; dementia in other diseases excluded	+	Recruited from longitudinal studies in period 1984-2013 (Alzheimer Disease Patient Registry, Alzheimer Disease Research Centre Study, and Mayo Clinic Study of Ageing); community dwelling persons aged 70-89 years; excluded structural brain lesions	+
Selection of controls	Community controls	Population controls; randomly selected from electoral role aged ≥65 years prior to extraction of health data for controls	+	Community controls from longitudinal study of ageing; individuals aged ≥65 years; selected if seen by physician in same month as clinical subject diagnosed; matched by age and sex	+
Definition of controls	No history of disease	Excluded if dementia read-code in records; no independent screening	+	Excluded if diagnosed with DLB/AD during the study, previous stroke, head injury, neurologic disease or movement disorder; extensive cognitive and medical examination	+
Comparability					
Comparability of cases and controls on basis of design and analysis	Study controls for the most important factor (+/-), and any additional factor (+/-)	Controls for age, sex, vascular risk factors (diabetes, IHD, AF, CVD, hypertension, hyperlipidaemia, heart failure and past or current smoking), head injury, alcohol dependence syndrome, and depression	+	Controls for age, sex; multivariate analyses control for family history, depression, APOE ε4 alleles, education level, head injury, cancer, and vascular risk factors (stroke, diabetes, alcohol, smoking)	+
Exposure					
Ascertainment of exposure	Secure record, structured interview by healthcare practitioner	Secure administrative health record, read-codes for mid-life factors documented between aged 30-65 years within years 1966-2009	+	Anxiety history from medical history section of medical record	+
Same method of ascertainment for cases and controls	Yes	Yes; review of risk factor read-codes	+	Yes; review of medical history	+
Non-response rate	Similar for both cases and controls	NR	-	NR	-
Total Score			7		8

(DLB = Dementia with Lewy bodies; NR = not recorded)

Table 3 Cohort studies: Newcastle-Ottawa scale for assessment of quality of included cohort studies
(+ / - represents whether individual criterion within the subsection was fulfilled)

	Acceptable Criteria	Petkus et al. 2016		Gallacher et al. 2009	
Selection					
Representativeness of exposed cohort	Representative of average adult in the community (age/sex)	Population based Swedish twin registry, subsample of twins aged ≥ 50 years	+	Men only, representative of male inhabitants of Caerphilly region	-
Selection of non-exposed cohort	Drawn from same community as exposed cohort	Drawn from same community as exposed cohort	+	Drawn from same community as exposed cohort	+
Ascertainment of exposure	Secured records, clinical diagnosis using diagnostic tools (ICD-10/DSM-V)	State anxiety subscale of the State-Trait Personality Inventory (STPI), containing a subset of items from the STAI	+	Structured interview using STAI	+
Demonstration that outcome of interest was not present at start of study	Assessment for dementia at initial enrolment	No baseline screening, exclusion if previous dementia diagnosis, age at inclusion (mean age 60.86 years) makes cognitive impairment unlikely	-	Age at inclusion (mean age 56.1 years) makes cognitive impairment unlikely	-
Comparability					
Comparability of cohorts on basis of design or analysis	Study controls for the most important factor (+), and for any additional factor (+)	Multivariate models control for depression symptoms, baseline age, sex, education, physical illness	+	Study controls for age, social class, marital status, vascular risk factors (alcohol consumption, BP, BMI, total cholesterol, previous vascular disease), educational ability (National Adult Reading Test), and depression symptoms (GHQ-30)	+
Exposure					
Assessment of outcome	Independent blind assessment, record linkage	Screening for dementia using MMSE, cognitive in-person testing (assessing a range of cognitive domains), DSM-III or IV, and record linkage using National Patient Registry and National Patient Cause of Death Registry	+	Cognitive function assessed using CAMDEX, FAB, CDR; diagnosis made using DSM-IV, screening of primary care and hospital records	+
Follow up adequate for outcome to occur	Follow up >10 years	28 years	+	>20 years	+
Adequacy of follow up of cohorts	Complete follow up, or subjects lost to follow-up unlikely to introduce bias	NR	-	20% lost to follow up	+
Total Score			7		7

(BMI = body mass index; BP = blood pressure; CAMDEX = Cambridge mental disorders of the elderly examination; CDR = clinical dementia rating; DSM III/IV/V = Diagnostic and statistical manual of mental disorders III/IV/V; FAB = frontal assessment battery; GHQ-30 = 30-item general health questionnaire; ICD-10 = International classification of diseases 10; MMSE = mini mental state examination; NR = not recorded; STAI = State trait anxiety inventory)



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6,7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2, 9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7,17
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6,7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10,19,20
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10,19,20
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8,9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12,13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11,12,13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Support for mid-life anxiety diagnosis as an independent risk factor for dementia: a systematic review.

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Geriatric medicine, Neurology
Keywords:	Dementia < NEUROLOGY, Anxiety disorders < PSYCHIATRY, EPIDEMIOLOGY

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3 **Support for mid-life anxiety diagnosis as an independent risk factor for**
4 **dementia: a systematic review.**
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Abstract

Objectives: Anxiety is an increasingly recognised predictor of cognitive deterioration in older adults and those with mild cognitive impairment (MCI). Often believed to be a prodromal feature of neurodegenerative disease, anxiety may also be an independent risk factor for dementia, operationally defined here as preceding dementia diagnosis by >10 years.

Design: A systematic review of the literature on anxiety diagnosis and long-term risk for dementia was performed following published guidelines.

Setting and participants: MEDLINE, PSYCINFO, and EMBASE were searched for peer-reviewed journals up until 8 March 2017. Publications reporting hazard/odds ratios for all-cause dementia based on clinical criteria from prospective cohort or case-control studies were selected. Included studies measured clinically significant anxiety in isolation or after controlling for symptoms of depression, and reported a mean interval between anxiety assessment and dementia diagnosis of at least 10 years. Methodological quality assessments were performed using the Newcastle-Ottawa scale.

Outcome measure: HR/ORs for all cause dementia.

Results Searches yielded 3510 articles, of which four (0.02%) were eligible. The studies had a combined sample size of 29,819, and all studies found a positive association between clinically significant anxiety and future dementia. Due to the heterogeneity between studies, a meta-analysis was not conducted.

Conclusions Clinically significant anxiety in mid-life was associated with an increased risk of dementia over an interval of at least 10 years. These findings indicate that anxiety may be a risk factor for late-life dementia, excluding anxiety that is related to prodromal cognitive decline. With increasing focus on identifying modifiable risk factors for dementia, more high

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3 quality prospective studies are required to clarify whether clinical anxiety is a risk factor for
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5 dementia, separate from a prodromal symptom.
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8 **Strengths and limitations of this study:**

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11 • This systematic review used a rigorous methodology, with broad search terms and
12 precisely pre-defined inclusion and exclusion criteria to investigate a life-course
13 association between a potentially modifiable risk factor, anxiety, and dementia,
14 whilst excluding anxiety related to pre-clinical dementia.
15
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- 17 • Strict exclusion criteria were used to remove studies that did not either discuss
18 anxiety diagnosis alone or control for depression, to account for high levels of
19 anxiety-depression comorbidity
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- 22 • Study quality was formally investigated using the Newcastle-Ottawa scale
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- 25 • The review was limited by the lack of assessment of cognition at baseline in
26 retrospective studies, however, the length of look-back minimises the likelihood of
27 cognitive impairment at baseline
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- 30 • The small number and heterogeneity of study designs rendered a meta-analysis
31 inappropriate, therefore formal statistical analyses could not be performed
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44 **Introduction**

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46 Dementia, and more specifically Alzheimer's disease (AD), is a progressive neurocognitive
47 disease. In the absence of any disease modifying treatments, there is increasing focus on
48 primary prevention to reduce risk of its development, and on early intervention to
49 potentially slow progression. A better understanding of risk factors for dementia is
50 therefore vital for improving therapeutic interventions. Alongside a number of well
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3 described cardiovascular risk factors [1], increasing evidence has highlighted the association
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5 between psychiatric illnesses and the development of late-onset dementia [2]. Further work
6
7 is needed to understand whether these psychiatric symptoms and illnesses represent
8
9 prodromal symptoms or act as independent risk factors.
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12 Depression has been consistently related to the development of dementia [3]. Three meta-
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14 analyses have reported that a diagnosis of depression is associated with up to a twofold
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16 increase in risk [3–5]. Ownby and colleagues further report that a longer interval between
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18 diagnosis of depression and diagnosis of dementia is significantly associated with an
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20 increased odds ratio (OR) of developing dementia [3]. This substantiates interpretations of
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22 depression as a risk factor for developing dementia, whereas a stronger association over
23
24 shorter intervals would have been more indicative of prodromal symptoms. Conversely, a
25
26 recent study found no association between dementia and depressive symptoms
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28 experienced more than 22 years before dementia diagnosis, however a positive association
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30 between dementia and depressive symptoms experienced on average 11 years prior to
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32 diagnosis of dementia was reported [6].
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38 Although anxiety is a prevalent psychiatric disorder [7], and commonly co-occurs with
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40 depression, the impact of anxiety on risk for cognitive decline and dementia has been far
41
42 less studied. Anxiety symptoms are commonly experienced in the years preceding a
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44 dementia diagnosis [8], and have been associated with cognitive decline and the
45
46 progression from MCI to AD [9–11]. A recent review reported that anxiety and
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48 neuropsychiatric symptoms not reaching clinically diagnostic levels were associated with
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50 increased risk of dementia [12]. The authors indicated that anxiety was likely a prodromal
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52 symptom of dementia in these community samples. This may well have been the case,
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3 particularly given the relatively short intervals between assessment of anxiety symptoms
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5 and assessment of dementia, however, this does not preclude anxiety also being a risk
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7 factor.
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10 The association between anxiety symptoms (independent of the dementia-prodrome) and
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12 dementia in later life could more easily be investigated with longer intervals between
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14 anxiety assessment and dementia diagnosis, as the studies that have investigated this
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16 association within a 5-10 year interval have reported variable results [13,14]. The average
17
18 length of prodromal preclinical cognitive decline has been proposed to be between 5-6
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20 years [15], and individuals diagnosed with MCI may progress to AD within 5 years [16].
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22 Therefore, examining studies with at least a 10-year interval between anxiety assessment
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24 and dementia diagnosis would increase likelihood that anxiety is independent from the
25
26 dementia prodrome.
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31 It is possible that anxiety symptoms meeting diagnostic threshold will have a stronger
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33 association with dementia than general symptoms because this has been shown with
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35 depression [4]. To date, there has been no systematic review to investigate the association
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37 between clinically significant anxiety and dementia. The aim of this study was therefore to
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39 review the literature examining the association between clinically significant levels of
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41 anxiety and dementia risk over a longer timescale (>10 years).
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45 **Methods**

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48 This systematic review followed the Preferred Reporting Items for Systematic Reviews and
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50 Meta-analyses (PRISMA) and Centre for Reviews and Dissemination (CRD) guidance for
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52 undertaking reviews in health care [17].
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Search strategy

A systematic literature search of MEDLINE, PSYCINFO and EMBASE databases was conducted of articles published from inception up until 8th March 2017 to identify articles reporting analyses of the association between anxiety (as defined by clinical diagnosis or self-report scales with a clinically significant threshold) and dementia or MCI incidence. Search terms used consisted of: (dement* OR Alzheimer* OR “mild cognitive impairment” OR MCI) AND (anx* OR “generalised anxiety disorder” OR GAD) AND (risk* OR odds), as presented in online supplementary table ST1. We aimed to identify articles discussing (1) diagnosis of any type of dementia, (2) anxiety diagnosis, and (3) risk of dementia. The search was restricted to human studies and those published in English. Reference lists were searched for additional relevant articles. Searches were conducted by a single reviewer (AG). An independent review of all screened articles was conducted by a second reviewer (MS). Any disagreement was resolved by consensus with a third reviewer (NM), which occurred in two cases.

Selection Criteria and Article Screening

Inclusion criteria were 1) a diagnosis of anxiety or an assessment of anxiety symptoms meeting diagnostic criteria using a standardised assessment tool, excluding populations with post-traumatic stress disorder (PTSD) or obsessive-compulsive disorder (OCD); 2) population-based studies where anxiety is assessed at least – on average – 10 years preceding final clinical assessment for dementia in line with previous meta-analyses on depression using intervals of at least 10 years [3]; 3) a diagnosis of dementia using validated criteria (e.g. Diagnostic Statistical Manual III-IV (DSM III-IV), International Classification of Diseases 10 (ICD-10)); 4) late-onset dementia diagnoses (aged ≥ 65 years). Eligible articles were identified by performing an initial screen of titles and abstracts, followed by a full

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3 article review of those that passed screening. All retrospective and prospective studies that
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5 met these criteria were selected.
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7 8 *Data extraction* 9

10 Outcome measures related to anxiety and dementia diagnosis were independently
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12 extracted by two authors (AG, MS). Disagreements were resolved through discussion. Study
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14 design, sample characteristics (including educational level and age), follow-up length,
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16 dropout rate, anxiety (including measure and baseline score where appropriate), criteria for
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18 assessing dementia, and measurements of depression as a confounder (including measure
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20 and baseline score), were recorded. In cases of insufficient data, authors were contacted by
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22 email.
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29 30 *Study Quality* 31

32 Two authors (AG, MS) independently assessed study quality and risk of bias using the
33
34 Newcastle-Ottawa scale, which contains separate quality assessment instruments for case-
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36 control and cohort studies.
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39 40 **Results**

41 42 *Literature Search* 43

44 The literature search detected 3509 citations, of which two were duplicates. One further
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46 paper was identified manually during reference screening. After screening titles and
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48 abstracts, 18 full-text articles were assessed for eligibility. Fourteen articles were excluded
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50 based on criteria described earlier (Figure 1), four studies were included in the final review
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52 [18–21].
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Study Characteristics

Characteristics of the four selected studies are shown in Table 1. Clinically significant anxiety was documented based on clinical diagnosis using International Classification of Diseases 10 (ICD-10) criteria (n = 2), the State Trait Anxiety Inventory (STAI, n = 1) and a subscale of the State Trait Personality Inventory (STPI, n = 1).

Gallacher et al. (2009) measured anxiety using the STAI, which has a range from 20 to 80 [22], and is a validated measure for assessing anxiety symptoms. A clinically significant cut-off of 39-40 has been proposed [23,24]. Gallacher et al. (2009) categorised 'high anxiety' as having a STAI score between 35 and 72, compared to a 'low anxiety' group who had a STAI score between 20 and 34. Boot et al. (2013) and Zilkens et al. (2014) used ICD-10 criteria to diagnose an anxiety disorder.

Petkus et al. (2016) assessed anxiety using state anxiety subscale of the State-Trait Personality Inventory (STPI), which contains a subset of items from the STAI. Participants scoring at least one standard deviation above the population mean, equating to a score of ≥ 25 out of 40, were categorised having 'high anxiety'. Although there is no established cut-off for clinically significant anxiety using this scale, scores greater than 1 SD above the population mean are likely to represent a group with a high anxiety symptom burden. After discussion amongst the reviewers (AG, MS, NLM), we reached a consensus judgement that the study was suitable for inclusion in this review.

Dementia diagnosis was in most cases assessed using DSM III-IV (n = 2) or ICD-10 criteria (n = 1), although the study by Boot et al. (2013) assessed Dementia with Lewy Bodies (DLB) by clinical diagnosis using published criteria [25].

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3 Sample sizes of the studies ranged from 441 to 27 136 participants, recruited from both or
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5 either community and hospital inpatient/outpatient populations. Gallacher et al. (2009) and
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7 Petkus et al. (2016) conducted prospective cohort studies using a community twin-
8
9 population that excluded dementia at baseline. Zilkens et al. (2014), and Boot et al. (2013)
10
11 conducted matched case-control studies, which retrospectively analysed community and
12
13 hospital records of individuals with dementia or case-matched controls for anxiety diagnosis
14
15 and therefore did not include a cognitive assessment at baseline to exclude dementia.
16
17 Zilkens et al. (2014) drew controls from the electoral roll, whereas Boot et al. (2013) drew
18
19 them from the community-dwelling persons included in the Mayo Clinic Study of Aging. The
20
21 proportion of females in each study ranged from 0 to 56.6%. Educational level was recorded
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23 for all but one study; which ranged from 55% with no qualifications to 95% with >9 years of
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25 education.
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31 INSERT TABLE 1
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34 *Anxiety diagnosis association with dementia* 35

36 All studies included in this review found a significant increase in the number of dementia
37
38 diagnoses in patients who had a clinical anxiety diagnosis or experienced clinically significant
39
40 anxiety symptoms on average at least 10 years prior to their diagnosis of dementia; Zilkens
41
42 et al. (2014): OR = 1.61 (95% CI 1.28-2.02), Boot et al. (2013): OR = 7.4 (95% CI 3.5-16),
43
44 Gallacher et al. (2009): OR = 1.62 (95% CI 0.59-4.41) and Petkus et al. (2016): OR = 1.48 (95%
45
46 CI 1.01-2.18), respectively [18–21]. On the whole, retrospective studies that looked back for
47
48 life-long diagnoses of anxiety found a stronger association between mid-life anxiety and
49
50 later dementia diagnosis, than prospective studies investigating an association over a
51
52 shorter time period. Additionally, Petkus et al. (2016) demonstrated that the association
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3 between high anxiety and dementia diagnosis remained when they excluded participants
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5 who developed dementia within 5 years of the baseline assessment. This subsample had an
6
7 average interval between baseline and dementia diagnosis of 14.7 years (SD 6.7 years). Both
8
9 lend support that the associations found were independent of prodromal dementia
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11
12 symptoms.

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14
15 Each study controlled for a range of demographic factors, with all controlling for vascular
16
17 and other psychiatric risk factors (Table 2 and 3). All studies assessed and controlled for
18
19 depression symptoms in their analysis. Boot et al. (2013) found a stronger association
20
21 between anxiety diagnosis alone with future dementia than either depression diagnosis
22
23 alone or mixed anxiety and depression diagnosis, although the number of individuals with
24
25 anxiety was markedly larger than those in the other two categories (anxiety alone n=168;
26
27 depression alone n=52; anxiety and depression n=56). Although Zilkens et al. (2014)
28
29 assessed a range of psychiatric diagnoses including anxiety and depression, they did not
30
31 assess their interaction. Petkus et al. (2016) and Gallacher et al. (2009), whilst controlling for
32
33 depression, made no assessment of the comparative strength of relationship or their
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35 interaction.
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40 *Study Quality Rating*

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43 All studies included were rated highly on the Newcastle-Ottawa scale [26]. From a maximum
44
45 score of 9, Boot et al (2013) was rated 8; and Zilkens et al. (2014), Petkus et al. (2016) and
46
47 Gallacher et al. (2009) were each rated 7. These studies were of similar quality to those
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49 included in a recent meta-analysis examining dementia risk estimates associated with late-
50
51 life depression [4].
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3 Three of the studies had representative samples of community populations; the fourth led
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5 by Gallacher et al. (2009) included only men. All controlled for a range of both demographic,
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7 physical and psychological health factors. All outcomes were assessed either via secure
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9 health records, or independent validation. Gallacher et al. (2009) experienced 20% loss to
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11 follow-up, which compares favourably to the pre-mentioned Cherbain et al. (2015) review,
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13 which considered studies with an attrition rate of between 4.3% and 55.46%, and a review
14
15 of MCI drug studies with attrition rates varying from 12% to 49% [27]. Petkus et al. (2016)
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17 did not clearly report loss to follow-up. For both case-control studies, the primary care
18
19 records did not include a cognitive assessment at baseline. Therefore, pre-existing cognitive
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21 impairment before diagnosis cannot be ruled out, although long look-back periods make this
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23 less likely.
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31 INSERT TABLE 3

32 33 34 **Discussion**

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36 This systematic review found four high quality studies that all showed a positive association
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38 between clinically significant anxiety and risk of late-onset dementia over a mean interval of
39
40 at least 10 years from anxiety assessment to dementia diagnosis, even after accounting for
41
42 potential confounders. This important finding provides further evidence that a common
43
44 mental health condition in mid-life is associated with later life neurodegenerative disorders.
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48 Anxiety symptomatology has previously been related to dementia risk and cognitive decline,
49
50 although not conclusively [10,28]. A recent systematic review reported a positive
51
52 association between anxiety symptoms and dementia diagnosis over a short time interval
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54 [12]. In that review the majority of studies reported follow up periods between 2-3.8 years.
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3 A single study had a follow up time of up to 11.8 years, however the average interval
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5 between anxiety and dementia diagnosis may have been less than 10 years, therefore it was
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7 not included in the current review [13]. Gulpers et al. found stronger associations with
8
9 smaller intervals between assessment of anxiety and dementia diagnosis. As a result, the
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11 authors concluded that anxiety may result from a prodromal state of dementia, where an
12
13 increase in anxiety may be due to an individual's insight into their early, subjective
14
15 experience of cognitive decline [12]. Given the short time interval between assessments,
16
17 Gulpers et al. were unable to determine whether anxiety could also serve as an independent
18
19 risk for dementia. This review reports solely articles that were not included Gulpers et al.'s
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21 analyses, and therefore furthers their work by providing an independent assessment of the
22
23 anxiety-dementia association. Effect sizes of the studies included in this review (1.48 - 7.4)
24
25 were comparable to the overall effect size found by Gulpers et al. (2016) of 1.61, suggesting
26
27 that the association between clinically significant mid-life anxiety and later-life dementia is
28
29 as strong as that between late-life anxiety symptoms and dementia.
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35 The prodromal phase of dementia can begin several years before objective dementia is
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37 manifest. In the present review, we sought to minimise the potential influence of pre-
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39 clinical cognitive decline by including only studies that assessed anxiety and dementia
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41 diagnoses over an extended period. Three studies (Zilkens et al. 2014; Gallacher et al. 2009;
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43 Petkus et al. 2016) demonstrated a mean interval of at least 10 years between the anxiety
44
45 and dementia evaluations. Boot et al. (2013) analysed participant's lifelong medical record,
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47 however, the mean interval between anxiety and dementia diagnosis was not reported.
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51 Findings from this review corroborate recent evidence that anxiety symptoms or diagnosis
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53 are associated with risk of MCI [29,30]. These findings further complement the association
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3 between depression and dementia diagnosis [4], which is particularly relevant due to high
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5 levels of anxiety-depression comorbidity. Moreover, they lend support for the proposal that
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7 multiple psychiatric risk factors are implicated together as a latent risk factor for dementia
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9
10 [2].

11
12 It has recently been suggested that a longer interval period between anxiety and dementia
13
14 diagnosis may provide evidence for a common biological pathway linking anxiety,
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16 depression, and dementia [20]. An abnormal stress response, such as exhibited in anxiety
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18 disorders, may be associated with accelerated cellular ageing and neuro-progression (a
19
20 pathological reorganisation of the central nervous system) resulting in increased
21
22 neurodegeneration, neuronal apoptosis and lowered neuroplasticity [31]. Although
23
24 glucocorticoid, inflammatory mediator and vascular disease mechanisms are hypothesised
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26 [3,32], as yet, no convincing candidate biological mechanism linking anxiety and cognitive
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28 impairment exists.
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34 The results of this review should be interpreted in the light of their limitations. Only studies
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36 that had been published and written in English were included, which may limit extrapolation
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38 across broader populations. Retrospective studies did not examine baseline cognition and
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40 therefore cannot exclude early cognitive decline at the time of anxiety assessment,
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42 however, the length of look-back, ranging from over 10 years to the first entry of an
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44 individual's medical record, minimises the likelihood of cognitive impairment at baseline. To
45
46 account for high levels of anxiety-depression comorbidity, this review included only papers
47
48 discussing anxiety diagnosis alone, or those that controlled for depression symptomatology.
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50
51 However, the Zilkens et al. (2014) and Boot et al. (2013) cannot completely exclude overlap
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53
54 of these two commonly comorbid illnesses because their occurrence was ascertained from
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3 lists of diagnoses in medical records. The use of read codes in retrospective studies may
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5 have resulted in lower identification of individuals with clinically significant anxiety as a
6
7 result of inconsistent entry of read codes during evaluations, or of absence of clinical record
8
9 for non-help seekers [33]. Publication bias may also have influenced the studies included, as
10
11 positive findings may be more likely to have been published than studies finding no
12
13 association. Furthermore, results must be interpreted in the light of proposals that the
14
15 prodromal AD pathophysiologic processes may develop beyond 10 years before the onset of
16
17 clinical symptoms [34].

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22 Whether reducing anxiety in middle-age would result in reduced risk of dementia remains
23
24 an open question. The effect of treatment of anxiety using pharmacologic and non-
25
26 pharmacologic therapies during midlife on later risk for dementia has not yet been
27
28 investigated. Benzodiazepines, commonly used in the treatment of anxiety, have been
29
30 shown to increase risk of mortality in some groups [35]. It is possible that diverse non-
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32 pharmacological therapies, including talking therapies [36] and mindfulness-based
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34 interventions and meditation practices [37], that are known to reduce anxiety in midlife,
35
36 could have a risk-reducing effect, although this is yet to be thoroughly researched.
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41 Given the high prevalence of anxiety seen in primary care, we suggest that general
42
43 practitioners could consider anxiety alongside depression as an indicator of risk factor for
44
45 dementia. To improve the rate of earlier diagnosis of dementia, close monitoring of subtle
46
47 cognitive decline in older adults with a history of anxiety, depression and cerebrovascular
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49 disease would be encouraged. This review expands our understanding of anxiety as a
50
51 potentially modifiable risk for dementia. Given the limited number of studies investigating
52
53 the anxiety-dementia relationship, further research is required to assess underlying
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3 mechanisms that link these disorders, and to disambiguate anxiety's potential role as a risk
4
5 factor as separate from a prodromal symptom of dementia.
6
7

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9
10
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25 **Contributors**

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28 AG contributed to design of the study, data screening and extraction, drafting of the
29
30 manuscript and submission. MS contributed to literature search, data screening and
31
32 extraction, and manuscript preparation. JDH contributed to the study design, provided
33
34 methodological expertise and editing of the manuscript. NLM contributed to the
35
36 conception and study design, data interpretation, and editing of the manuscript.
37
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40 **Competing interests**

41
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43 None of the contributing authors have any conflicting interests to declare.
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47 **Data sharing statement**

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50 No additional data are available.
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Figure 1 Flowchart of the search and study selection process; * = manually identified from Petkus et al. (2016)

Table 1 Study Characteristics

	Study type and setting; location	Follow-up/ Look back period; years (SD)	Mean age years (SD)	Female n (%)	Education level; no. (%)	Drop-out rate/Non-response rate %	Baseline cognition measure	Anxiety measure; cut-off	Baseline anxiety, %	Controls for depression; baseline depression measure	Dementia diagnosis; criteria (no. cases); OR/HR (95% CI)
Boot et al. 2013 (n=441)	Population based matched case-controlled, Mayo Clinic Rochester, Minnesota, USA	Lifelong diagnoses documented by medical record	72.5 (7.3) – DLB cases age at diagnosis	103 (23.1)	>9 yrs education; (95)	NR	NR	Clinical diagnosis, present in medical history section of medical record	23, 27% cases; 14, 5% controls	Yes; clinical diagnosis from medical history record	DLB diagnosis by behavioural neurologist; published criteria by McKeith et al (2005) (n=147); OR 7.4 (3.5-16)
Gallacher et al. 2009 (n=1160)	Prospective, community based cohort; Caerphilly, Wales, UK	Mean follow up period; 17.3 (1.3)	56.1 (4.4) – mean age at inclusion	0	no qualifications; 601 (55)	20	NR; dementia unlikely at inclusion (mean age <60 yrs)	STAI; score of ≥35	585, 50%	Yes; GHQ-30	Dementia diagnosis; DSM-IV or medical records (n=90); OR 1.62 (0.59-4.41)
Petkus et al. 2016 (n=1082)	Prospective, community based cohort; Swedish twins drawn from Swedish Twin Registry, Sweden	Follow up period; 28 (0)	60.86 (11.15) – mean age at inclusion	612 (56.6)	Beyond elementary education; 423 (39)	29.8	MMSE	State anxiety subscale of STPI; STPI > 1 SD Q1-Q4 (assessments over 4 time-points)	403, 37%	Yes; OARS depression subscale, CES-D	Dementia diagnosis; DSM-III or DMS-IV (n=172); HR 1.48 (1.01-2.18)
Zilkens et al. 2014 (n=27136)	Population based matched case-controlled, Western Australia	Mean look back period; cases 20.4 (10.4), controls 20.0 (10.3)	78.7 (4.7) – mean age at final time point	15359 (56.6)	NR	6.17 (excluded individuals)	NR	Clinical diagnosis using ICD-10 AM (Australian Modification) codes documented in health records; meeting diagnostic threshold	379, 2.8% cases	Yes; clinical diagnosis by GP	Dementia diagnosis; ICD-10 (n=13568); OR 1.61 (1.28-2.02) (>10 years look back period)

(CES-D = Centre of Epidemiological Studies depression subscale, DLB = Dementia with Lewy bodies, GHQ-30 = 30-item general health questionnaire, NR = not recorded; OARS = older American resources and services; STAI = State trait anxiety inventory; STPI = State trait personality inventory)

Table 2 Case controlled studies: Newcastle-Ottawa scale for assessment of quality of included case controlled studies (+ / - represents whether individual criterion within the subsection was fulfilled)

	Acceptable Criteria	Zilkens et al. 2014		Boot et al. 2013	
Selection					
Case definition	With independent validation	Record linkage from Western Australian Data Linkage System and Death Registry, no independent validation	-	Assessment for DLB using behavioural neurologist	+
Representativeness of cases	Consecutive or representative series of cases	All dementia cases in period 2000-2009 identified via read-code; lower limit index dementia age 65 years, upper limit 84 years; dementia in other diseases excluded	+	Recruited from longitudinal studies in period 1984-2013 (Alzheimer Disease Patient Registry, Alzheimer Disease Research Centre Study, and Mayo Clinic Study of Ageing); community dwelling persons aged 70-89 years; excluded structural brain lesions	+
Selection of controls	Community controls	Population controls; randomly selected from electoral role aged ≥65 years prior to extraction of health data for controls	+	Community controls from longitudinal study of ageing; individuals aged ≥65 years; selected if seen by physician in same month as clinical subject diagnosed; matched by age and sex	+
Definition of controls	No history of disease	Excluded if dementia read-code in records; no independent screening	+	Excluded if diagnosed with DLB/AD during the study, previous stroke, head injury, neurologic disease or movement disorder; extensive cognitive and medical examination	+
Comparability					
Comparability of cases and controls on basis of design and analysis	Study controls for the most important factor (+/-), and any additional factor (+/-)	Controls for age, sex, vascular risk factors (diabetes, IHD, AF, CVD, hypertension, hyperlipidaemia, heart failure and past or current smoking), head injury, alcohol dependence syndrome, and depression	+	Controls for age, sex; multivariate analyses control for family history, depression, APOE ε4 alleles, education level, head injury, cancer, and vascular risk factors (stroke, diabetes, alcohol, smoking)	+
Exposure					
Ascertainment of exposure	Secure record, structured interview by healthcare practitioner	Secure administrative health record, read-codes for mid-life factors documented between aged 30-65 years within years 1966-2009	+	Anxiety history from medical history section of medical record	+
Same method of ascertainment for cases and controls	Yes	Yes; review of risk factor read-codes	+	Yes; review of medical history	+
Non-response rate	Similar for both cases and controls	NR	-	NR	-
Total Score			7		8

(DLB = Dementia with Lewy bodies; NR = not recorded)

Table 3 Cohort studies: Newcastle-Ottawa scale for assessment of quality of included cohort studies
(+ / - represents whether individual criterion within the subsection was fulfilled)

	Acceptable Criteria	Petkus et al. 2016		Gallacher et al. 2009	
Selection					
Representativeness of exposed cohort	Representative of average adult in the community (age/sex)	Population based Swedish twin registry, subsample of twins aged ≥ 50 years	+	Men only, representative of male inhabitants of Caerphilly region	-
Selection of non-exposed cohort	Drawn from same community as exposed cohort	Drawn from same community as exposed cohort	+	Drawn from same community as exposed cohort	+
Ascertainment of exposure	Secured records, clinical diagnosis using diagnostic tools (ICD-10/DSM-V)	State anxiety subscale of the State-Trait Personality Inventory (STPI), containing a subset of items from the STAI	+	Structured interview using STAI	+
Demonstration that outcome of interest was not present at start of study	Assessment for dementia at initial enrolment	No baseline screening, exclusion if previous dementia diagnosis, age at inclusion (mean age 60.86 years) makes cognitive impairment unlikely	-	Age at inclusion (mean age 56.1 years) makes cognitive impairment unlikely	-
Comparability					
Comparability of cohorts on basis of design or analysis	Study controls for the most important factor (+), and for any additional factor (+)	Multivariate models control for depression symptoms, baseline age, sex, education, physical illness	+	Study controls for age, social class, marital status, vascular risk factors (alcohol consumption, BP, BMI, total cholesterol, previous vascular disease), educational ability (National Adult Reading Test), and depression symptoms (GHQ-30)	+
Exposure					
Assessment of outcome	Independent blind assessment, record linkage	Screening for dementia using MMSE, cognitive in-person testing (assessing a range of cognitive domains), DSM-III or IV, and record linkage using National Patient Registry and National Patient Cause of Death Registry	+	Cognitive function assessed using CAMDEX, FAB, CDR; diagnosis made using DSM-IV, screening of primary care and hospital records	+
Follow up adequate for outcome to occur	Follow up >10 years	28 years	+	>20 years	+
Adequacy of follow up of cohorts	Complete follow up, or subjects lost to follow-up unlikely to introduce bias	NR	-	20% lost to follow up	+
Total Score			7		7

(BMI = body mass index; BP = blood pressure; CAMDEX = Cambridge mental disorders of the elderly examination; CDR = clinical dementia rating; DSM III/IV/V = Diagnostic and statistical manual of mental disorders III/IV/V; FAB = frontal assessment battery; GHQ-30 = 30-item general health questionnaire; ICD-10 = International classification of diseases 10; MMSE = mini mental state examination; NR = not recorded; STAI = State trait anxiety inventory)

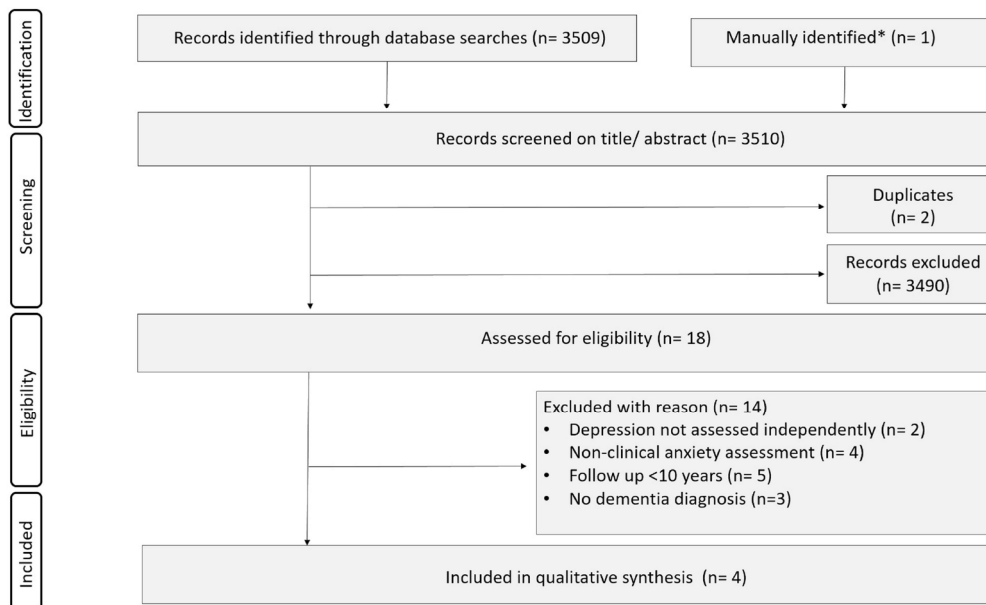


Figure 1 Flowchart of the search and study selection process; * = manually identified from Petkus et al. (2016)

175x106mm (300 x 300 DPI)

Example Search Strategy

Search carried out in Ovid MEDLINE(R) from 1946 to October Week 3 2017

#	Searches	Results
1	dement*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	101878
2	limit 1 to (english language and humans)	84635
3	alzheimer*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	123908
4	limit 3 to (english language and humans)	98174
5	mild cognitive impairment.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	10469
6	limit 5 to (english language and humans)	9789
7	MCI.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	12968
8	limit 7 to (english language and humans)	10517
9	2 OR 4 OR 6 OR 8	155363
10	anx*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	196896
11	limit 10 to (english language and humans)	154215
12	generalised anxiety disorder.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	475
13	limit 12 to (english language and humans)	438
14	GAD.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	7550
15	limit 14 to (english language and humans)	4299
16	11 OR 13 OR 15	156261
17	risk*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	2086806
18	limit 17 to (english language and humans)	1757965
19	odds.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	268449
20	limit 19 to (english language and humans)	257505
21	18 OR 20	1849508
22	9 AND 16 AND 21	776



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6,7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2, 9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7,17
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6,7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10,19,20
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10,19,20
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8,9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12,13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11,12,13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Page 2 of 2

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BMJ Open

Support for mid-life anxiety diagnosis as an independent risk factor for dementia: a systematic review.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019399.R2
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Date Submitted by the Author:	19-Jan-2018
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Geriatric medicine, Neurology
Keywords:	Dementia < NEUROLOGY, Anxiety disorders < PSYCHIATRY, EPIDEMIOLOGY

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3 **Support for mid-life anxiety diagnosis as an independent risk factor for**
4 **dementia: a systematic review.**
5
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7

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Abstract

Objectives: Anxiety is an increasingly recognised predictor of cognitive deterioration in older adults and those with mild cognitive impairment (MCI). Often believed to be a prodromal feature of neurodegenerative disease, anxiety may also be an independent risk factor for dementia, operationally defined here as preceding dementia diagnosis by >10 years.

Design: A systematic review of the literature on anxiety diagnosis and long-term risk for dementia was performed following published guidelines.

Setting and participants: MEDLINE, PSYCINFO, and EMBASE were searched for peer-reviewed journals up until 8 March 2017. Publications reporting hazard/odds ratios for all-cause dementia based on clinical criteria from prospective cohort or case-control studies were selected. Included studies measured clinically significant anxiety in isolation or after controlling for symptoms of depression, and reported a mean interval between anxiety assessment and dementia diagnosis of at least 10 years. Methodological quality assessments were performed using the Newcastle-Ottawa scale.

Outcome measure: HR/ORs for all cause dementia.

Results Searches yielded 3510 articles, of which four (0.02%) were eligible. The studies had a combined sample size of 29,819, and all studies found a positive association between clinically significant anxiety and future dementia. Due to the heterogeneity between studies, a meta-analysis was not conducted.

Conclusions Clinically significant anxiety in mid-life was associated with an increased risk of dementia over an interval of at least 10 years. These findings indicate that anxiety may be a risk factor for late-life dementia, excluding anxiety that is related to prodromal cognitive decline. With increasing focus on identifying modifiable risk factors for dementia, more high

1
2
3 quality prospective studies are required to clarify whether clinical anxiety is a risk factor for
4
5 dementia, separate from a prodromal symptom.
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7

8 **Strengths and limitations of this study:**

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- 10
11 • This systematic review used a rigorous methodology, with broad search terms and
12 precisely pre-defined inclusion and exclusion criteria to investigate a life-course
13 association between a potentially modifiable risk factor, anxiety, and dementia,
14 whilst excluding anxiety related to pre-clinical dementia.
15
16
- 17 • Strict exclusion criteria were used to remove studies that did not either discuss
18 anxiety diagnosis alone or control for depression, to account for high levels of
19 anxiety-depression comorbidity
20
21
- 22 • Study quality was formally investigated using the Newcastle-Ottawa scale
23
24
- 25 • The review was limited by the lack of assessment of cognition at baseline in
26 retrospective studies, however, the length of look-back minimises the likelihood of
27 cognitive impairment at baseline
28
29
- 30 • The small number and heterogeneity of study designs rendered a meta-analysis
31 inappropriate, therefore formal statistical analyses could not be performed
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44 **Introduction**

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46 Dementia, and more specifically Alzheimer's disease (AD), is a progressive neurocognitive
47 disease. In the absence of any disease modifying treatments, there is increasing focus on
48 primary prevention to reduce risk of its development, and on early intervention to
49 potentially slow progression. A better understanding of risk factors for dementia is
50 therefore vital for improving therapeutic interventions. Alongside a number of well
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3 described cardiovascular risk factors [1], increasing evidence has highlighted the association
4
5 between psychiatric illnesses and the development of late-onset dementia [2]. Further work
6
7 is needed to understand whether these psychiatric symptoms and illnesses represent
8
9 prodromal symptoms or act as independent risk factors.
10

11
12 Depression has been consistently related to the development of dementia [3]. Three meta-
13
14 analyses have reported that a diagnosis of depression is associated with up to a twofold
15
16 increase in risk [3–5]. Ownby and colleagues further report that a longer interval between
17
18 diagnosis of depression and diagnosis of dementia is significantly associated with an
19
20 increased odds ratio (OR) of developing dementia [3]. This substantiates interpretations of
21
22 depression as a risk factor for developing dementia, whereas a stronger association over
23
24 shorter intervals would have been more indicative of prodromal symptoms. Conversely, a
25
26 recent study found no association between dementia and depressive symptoms
27
28 experienced more than 22 years before dementia diagnosis, however a positive association
29
30 between dementia and depressive symptoms experienced on average 11 years prior to
31
32 diagnosis of dementia was reported [6].
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38 Although anxiety is a prevalent psychiatric disorder [7], and commonly co-occurs with
39
40 depression, the impact of anxiety on risk for cognitive decline and dementia has been far
41
42 less studied. Anxiety symptoms are commonly experienced in the years preceding a
43
44 dementia diagnosis [8], and have been associated with cognitive decline and the
45
46 progression from MCI to AD [9–11]. A recent review reported that anxiety and
47
48 neuropsychiatric symptoms not reaching clinically diagnostic levels were associated with
49
50 increased risk of dementia [12]. The authors indicated that anxiety was likely a prodromal
51
52 symptom of dementia in these community samples. This may well have been the case,
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1
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3 particularly given the relatively short intervals between assessment of anxiety symptoms
4
5 and assessment of dementia, however, this does not preclude anxiety also being a risk
6
7 factor.
8
9

10 The association between anxiety symptoms (independent of the dementia-prodrome) and
11
12 dementia in later life could more easily be investigated with longer intervals between
13
14 anxiety assessment and dementia diagnosis, as the studies that have investigated this
15
16 association within a 5-10 year interval have reported variable results [13,14]. The average
17
18 length of prodromal preclinical cognitive decline has been proposed to be between 5-6
19
20 years [15], and individuals diagnosed with MCI may progress to AD within 5 years [16].
21
22 Therefore, examining studies with at least a 10-year interval between anxiety assessment
23
24 and dementia diagnosis would increase likelihood that anxiety is independent from the
25
26 dementia prodrome.
27
28
29

30
31 It is possible that anxiety symptoms meeting diagnostic threshold will have a stronger
32
33 association with dementia than general symptoms because this has been shown with
34
35 depression [4]. To date, there has been no systematic review to investigate the association
36
37 between clinically significant anxiety and dementia. The aim of this study was therefore to
38
39 review the literature examining the association between clinically significant levels of
40
41 anxiety and dementia risk over a longer timescale (>10 years).
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44

45 **Methods**

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47
48 This systematic review followed the Preferred Reporting Items for Systematic Reviews and
49
50 Meta-analyses (PRISMA) and Centre for Reviews and Dissemination (CRD) guidance for
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52 undertaking reviews in health care [17].
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Search strategy

A systematic literature search of MEDLINE, PSYCINFO and EMBASE databases was conducted of articles published from inception up until 8th March 2017 to identify articles reporting analyses of the association between anxiety (as defined by clinical diagnosis or self-report scales with a clinically significant threshold) and dementia or MCI incidence. Search terms used consisted of: (dement* OR Alzheimer* OR “mild cognitive impairment” OR MCI) AND (anx* OR “generalised anxiety disorder” OR GAD) AND (risk* OR odds), as presented in online supplementary table ST1. We aimed to identify articles discussing (1) diagnosis of any type of dementia, (2) anxiety diagnosis, and (3) risk of dementia. The search was restricted to human studies and those published in English. Reference lists were searched for additional relevant articles. Searches were conducted by a single reviewer (AG). An independent review of all screened articles was conducted by a second reviewer (MS). Any disagreement was resolved by consensus with a third reviewer (NM), which occurred in two cases.

Selection Criteria and Article Screening

Inclusion criteria were 1) a diagnosis of anxiety or an assessment of anxiety symptoms meeting diagnostic criteria using a standardised assessment tool, excluding populations with post-traumatic stress disorder (PTSD) or obsessive-compulsive disorder (OCD); 2) population-based studies where anxiety is assessed at least – on average – 10 years preceding final clinical assessment for dementia in line with previous meta-analyses on depression using intervals of at least 10 years [3]; 3) a diagnosis of dementia using validated criteria (e.g. Diagnostic Statistical Manual III-IV (DSM III-IV), International Classification of Diseases 10 (ICD-10)); 4) late-onset dementia diagnoses (aged ≥ 65 years). Eligible articles were identified by performing an initial screen of titles and abstracts, followed by a full

1
2
3 article review of those that passed screening. All retrospective and prospective studies that
4
5 met these criteria were selected.
6

7 8 *Data extraction* 9

10 Outcome measures related to anxiety and dementia diagnosis were independently
11
12 extracted by two authors (AG, MS). Disagreements were resolved through discussion. Study
13
14 design, sample characteristics (including educational level and age), follow-up length,
15
16 dropout rate, anxiety (including measure and baseline score where appropriate), criteria for
17
18 assessing dementia, and measurements of depression as a confounder (including measure
19
20 and baseline score), were recorded. In cases of insufficient data, authors were contacted by
21
22 email.
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27 INSERT FIGURE 1
28

29 30 *Study Quality* 31

32 Two authors (AG, MS) independently assessed study quality and risk of bias using the
33
34 Newcastle-Ottawa scale, which contains separate quality assessment instruments for case-
35
36 control and cohort studies.
37
38

39 40 **Results** 41

42 43 *Literature Search* 44

45 The literature search detected 3509 citations, of which two were duplicates. One further
46
47 paper was identified manually during reference screening. After screening titles and
48
49 abstracts, 18 full-text articles were assessed for eligibility. Fourteen articles were excluded
50
51 based on criteria described earlier (Figure 1), four studies were included in the final review
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53 [18–21].
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Study Characteristics

Characteristics of the four selected studies are shown in Table 1. Clinically significant anxiety was documented based on clinical diagnosis using International Classification of Diseases 10 (ICD-10) criteria (n = 2), the State Trait Anxiety Inventory (STAI, n = 1) and a subscale of the State Trait Personality Inventory (STPI, n = 1).

Gallacher et al. (2009) measured anxiety using the STAI, which has a range from 20 to 80 [22], and is a validated measure for assessing anxiety symptoms. A clinically significant cut-off of 39-40 has been proposed [23,24]. Gallacher et al. (2009) categorised 'high anxiety' as having a STAI score between 35 and 72, compared to a 'low anxiety' group who had a STAI score between 20 and 34. Boot et al. (2013) and Zilkens et al. (2014) used ICD-10 criteria to diagnose an anxiety disorder.

Petkus et al. (2016) assessed anxiety using state anxiety subscale of the State-Trait Personality Inventory (STPI), which contains a subset of items from the STAI. Participants scoring at least one standard deviation above the population mean, equating to a score of ≥ 25 out of 40, were categorised having 'high anxiety'. Although there is no established cut-off for clinically significant anxiety using this scale, scores greater than 1 SD above the population mean are likely to represent a group with a high anxiety symptom burden. After discussion amongst the reviewers (AG, MS, NLM), we reached a consensus judgement that the study was suitable for inclusion in this review.

Dementia diagnosis was in most cases assessed using DSM III-IV (n = 2) or ICD-10 criteria (n = 1), although the study by Boot et al. (2013) assessed Dementia with Lewy Bodies (DLB) by clinical diagnosis using published criteria [25].

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2
3 Sample sizes of the studies ranged from 441 to 27 136 participants, recruited from both or
4
5 either community and hospital inpatient/outpatient populations. Gallacher et al. (2009) and
6
7 Petkus et al. (2016) conducted prospective cohort studies using a community twin-
8
9 population that excluded dementia at baseline. Zilkens et al. (2014), and Boot et al. (2013)
10
11 conducted matched case-control studies, which retrospectively analysed community and
12
13 hospital records of individuals with dementia or case-matched controls for anxiety diagnosis
14
15 and therefore did not include a cognitive assessment at baseline to exclude dementia.
16
17 Zilkens et al. (2014) drew controls from the electoral roll, whereas Boot et al. (2013) drew
18
19 them from the community-dwelling persons included in the Mayo Clinic Study of Aging. The
20
21 proportion of females in each study ranged from 0 to 56.6%. Educational level was recorded
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23 for all but one study; which ranged from 55% with no qualifications to 95% with >9 years of
24
25 education.
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31 INSERT TABLE 1
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34 *Anxiety diagnosis association with dementia*

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36 All studies included in this review found a significant increase in the number of dementia
37
38 diagnoses in patients who had a clinical anxiety diagnosis or experienced clinically significant
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40 anxiety symptoms on average at least 10 years prior to their diagnosis of dementia; Zilkens
41
42 et al. (2014): OR = 1.61 (95% CI 1.28-2.02), Boot et al. (2013): OR = 7.4 (95% CI 3.5-16),
43
44 Gallacher et al. (2009): OR = 1.62 (95% CI 0.59-4.41) and Petkus et al. (2016): OR = 1.48 (95%
45
46 CI 1.01-2.18), respectively [18–21]. On the whole, retrospective studies that looked back for
47
48 life-long diagnoses of anxiety found a stronger association between mid-life anxiety and
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50 later dementia diagnosis, than prospective studies investigating an association over a
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52 shorter time period. Additionally, Petkus et al. (2016) demonstrated that the association
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3 between high anxiety and dementia diagnosis remained when they excluded participants
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5 who developed dementia within 5 years of the baseline assessment. This subsample had an
6
7 average interval between baseline and dementia diagnosis of 14.7 years (SD 6.7 years). Both
8
9 lend support that the associations found were independent of prodromal dementia
10
11
12 symptoms.

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14
15 Each study controlled for a range of demographic factors, with all controlling for vascular
16
17 and other psychiatric risk factors (Table 2 and 3). All studies assessed and controlled for
18
19 depression symptoms in their analysis. Boot et al. (2013) found a stronger association
20
21 between anxiety diagnosis alone with future dementia than either depression diagnosis
22
23 alone or mixed anxiety and depression diagnosis, although the number of individuals with
24
25 anxiety was markedly larger than those in the other two categories (anxiety alone n=168;
26
27 depression alone n=52; anxiety and depression n=56). Although Zilkens et al. (2014)
28
29 assessed a range of psychiatric diagnoses including anxiety and depression, they did not
30
31 assess their interaction. Petkus et al. (2016) and Gallacher et al. (2009), whilst controlling for
32
33 depression, made no assessment of the comparative strength of relationship or their
34
35 interaction.
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40 *Study Quality Rating*

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43 All studies included were rated highly on the Newcastle-Ottawa scale [26]. From a maximum
44
45 score of 9, Boot et al (2013) was rated 8; and Zilkens et al. (2014), Petkus et al. (2016) and
46
47 Gallacher et al. (2009) were each rated 7. These studies were of similar quality to those
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49 included in a recent meta-analysis examining dementia risk estimates associated with late-
50
51 life depression [4].
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3 Three of the studies had representative samples of community populations; the fourth led
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5 by Gallacher et al. (2009) included only men. All controlled for a range of both demographic,
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7 physical and psychological health factors. All outcomes were assessed either via secure
8
9 health records, or independent validation. Gallacher et al. (2009) experienced 20% loss to
10
11 follow-up, which compares favourably to the pre-mentioned Cherbuin et al. (2015) review,
12
13 which considered studies with an attrition rate of between 4.3% and 55.46%, and a review
14
15 of MCI drug studies with attrition rates varying from 12% to 49% [27]. Petkus et al. (2016)
16
17 did not clearly report loss to follow-up. For both case-control studies, the primary care
18
19 records did not include a cognitive assessment at baseline. Therefore, pre-existing cognitive
20
21 impairment before diagnosis cannot be ruled out, although long look-back periods make this
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23 less likely.
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29 INSERT TABLE 2

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31 INSERT TABLE 3

32 33 34 **Discussion**

35
36 This systematic review found four high quality studies that all showed a positive association
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38 between clinically significant anxiety and risk of late-onset dementia over a mean interval of
39
40 at least 10 years from anxiety assessment to dementia diagnosis, even after accounting for
41
42 potential confounders. This important finding provides further evidence that a common
43
44 mental health condition in mid-life is associated with later life neurodegenerative disorders.
45
46

47
48 Anxiety symptomatology has previously been related to dementia risk and cognitive decline,
49
50 although not conclusively [10,28]. A recent systematic review reported a positive
51
52 association between anxiety symptoms and dementia diagnosis over a short time interval
53
54 [12]. In that review the majority of studies reported follow up periods between 2-3.8 years.
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3 A single study had a follow up time of up to 11.8 years, however the average interval
4
5 between anxiety and dementia diagnosis may have been less than 10 years, therefore it was
6
7 not included in the current review [13]. Gulpers et al. found stronger associations with
8
9 smaller intervals between assessment of anxiety and dementia diagnosis. As a result, the
10
11 authors concluded that anxiety may result from a prodromal state of dementia, where an
12
13 increase in anxiety may be due to an individual's insight into their early, subjective
14
15 experience of cognitive decline [12]. Given the short time interval between assessments,
16
17 Gulpers et al. were unable to determine whether anxiety could also serve as an independent
18
19 risk for dementia. This review reports solely articles that were not included Gulpers et al.'s
20
21 analyses, and therefore furthers their work by providing an independent assessment of the
22
23 anxiety-dementia association. Effect sizes of the studies included in this review (1.48 - 7.4)
24
25 were comparable to the overall effect size found by Gulpers et al. (2016) of 1.61, suggesting
26
27 that the association between clinically significant mid-life anxiety and later-life dementia is
28
29 as strong as that between late-life anxiety symptoms and dementia.
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35 The prodromal phase of dementia can begin several years before objective dementia is
36
37 manifest. In the present review, we sought to minimise the potential influence of pre-
38
39 clinical cognitive decline by including only studies that assessed anxiety and dementia
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41 diagnoses over an extended period. Three studies (Zilkens et al. 2014; Gallacher et al. 2009;
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43 Petkus et al. 2016) demonstrated a mean interval of at least 10 years between the anxiety
44
45 and dementia evaluations. Boot et al. (2013) analysed participant's lifelong medical record,
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47 however, the mean interval between anxiety and dementia diagnosis was not reported.
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52 Findings from this review corroborate recent evidence that anxiety symptoms or diagnosis
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54 are associated with risk of MCI [29,30]. These findings further complement the association
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3 between depression and dementia diagnosis [4], which is particularly relevant due to high
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5 levels of anxiety-depression comorbidity. Moreover, they lend support for the proposal that
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7 multiple psychiatric risk factors are implicated together as a latent risk factor for dementia
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10 [2].

11
12 It has recently been suggested that a longer interval period between anxiety and dementia
13
14 diagnosis may provide evidence for a common biological pathway linking anxiety,
15
16 depression, and dementia [20]. An abnormal stress response, such as exhibited in anxiety
17
18 disorders, may be associated with accelerated cellular ageing and neuro-progression (a
19
20 pathological reorganisation of the central nervous system) resulting in increased
21
22 neurodegeneration, neuronal apoptosis and lowered neuroplasticity [31]. Although
23
24 glucocorticoid, inflammatory mediator and vascular disease mechanisms are hypothesised
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26 [3,32], as yet, no convincing candidate biological mechanism linking anxiety and cognitive
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28 impairment exists.
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34 The results of this review should be interpreted in the light of their limitations. Only studies
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36 that had been published and written in English were included, which may limit extrapolation
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38 across broader populations. Retrospective studies did not examine baseline cognition and
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40 therefore cannot exclude early cognitive decline at the time of anxiety assessment,
41
42 however, the length of look-back, ranging from over 10 years to the first entry of an
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44 individual's medical record, minimises the likelihood of cognitive impairment at baseline. To
45
46 account for high levels of anxiety-depression comorbidity, this review included only papers
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48 discussing anxiety diagnosis alone, or those that controlled for depression symptomatology.
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51 However, the Zilkens et al. (2014) and Boot et al. (2013) cannot completely exclude overlap
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54 of these two commonly comorbid illnesses because their occurrence was ascertained from
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3 lists of diagnoses in medical records. The use of read codes in retrospective studies may
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5 have resulted in lower identification of individuals with clinically significant anxiety as a
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7 result of inconsistent entry of read codes during evaluations, or of absence of clinical record
8
9 for non-help seekers [33]. Publication bias may also have influenced the studies included, as
10
11 positive findings may be more likely to have been published than studies finding no
12
13 association. Furthermore, results must be interpreted in the light of proposals that the
14
15 prodromal AD pathophysiologic processes may develop beyond 10 years before the onset of
16
17 clinical symptoms [34].

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22 Whether reducing anxiety in middle-age would result in reduced risk of dementia remains
23
24 an open question. The effect of treatment of anxiety using pharmacologic and non-
25
26 pharmacologic therapies during midlife on later risk for dementia has not yet been
27
28 investigated. Benzodiazepines, commonly used in the treatment of anxiety, have been
29
30 shown to increase risk of mortality in some groups [35], and therefore cannot be considered
31
32 a measure to reduce dementia incidence in those with clinical anxiety. It is possible that
33
34 diverse non-pharmacological therapies, including talking therapies [36] and mindfulness-
35
36 based interventions and meditation practices [37], that are known to reduce anxiety in
37
38 midlife, could have a risk-reducing effect, although this is yet to be thoroughly researched.
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43 Given the high prevalence of anxiety seen in primary care, we suggest that general
44
45 practitioners could consider anxiety alongside depression as an indicator of risk factor for
46
47 dementia. To improve the rate of earlier diagnosis of dementia, close monitoring of subtle
48
49 cognitive decline in older adults with a history of anxiety, depression and cerebrovascular
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51 disease would be encouraged. This review expands our understanding of anxiety as a
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53 potentially modifiable risk for dementia. Given the limited number of studies investigating
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2
3 the anxiety-dementia relationship, further research is required to assess underlying
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5 mechanisms that link these disorders, and to disambiguate anxiety's potential role as a risk
6
7 factor as separate from a prodromal symptom of dementia.
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9

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24
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26

27 **Contributors**

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30 AG contributed to design of the study, data screening and extraction, drafting of the
31
32 manuscript and submission. MS contributed to literature search, data screening and
33
34 extraction, and manuscript preparation. JDH contributed to the study design, provided
35
36 methodological expertise and editing of the manuscript. NLM contributed to the
37
38 conception and study design, data interpretation, and editing of the manuscript.
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43 **Competing interests**

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46 None of the contributing authors have any conflicting interests to declare.
47
48

49 **Data sharing statement**

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52 No additional data are available.
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Figure 1 Flowchart of the search and study selection process; * = manually identified from Petkus et al. (2016)

Table 1 Study Characteristics

	Study type and setting; location	Follow-up/ Look back period; years (SD)	Mean age years (SD)	Female n (%)	Education level; no. (%)	Drop-out rate/Non-response rate %	Baseline cognition measure	Anxiety measure; cut-off	Baseline anxiety, %	Controls for depression; baseline depression measure	Dementia diagnosis; criteria (no. cases); OR/HR (95% CI)	
10 11 12	Boot et al. 2013 (n=441)	Population based matched case-controlled, Mayo Clinic Rochester, Minnesota, USA	Lifelong diagnoses documented by medical record	72.5 (7.3) – DLB cases age at diagnosis	103 (23.1)	>9 yrs education; (95)	NR	NR	Clinical diagnosis, present in medical history section of medical record	23, 27% cases; 14, 5% controls	Yes; clinical diagnosis from medical history record	DLB diagnosis by behavioural neurologist; published criteria by McKeith et al (2005) (n=147); OR 7.4 (3.5-16)
13 14 15 16	Gallacher et al. 2009 (n=1160)	Prospective, community based cohort; Caerphilly, Wales, UK	Mean follow up period; 17.3 (1.3)	56.1 (4.4) – mean age at inclusion	0	no qualifications; 601 (55)	20	NR; dementia unlikely at inclusion (mean age <60 yrs)	STAI; score of ≥35	585, 50%	Yes; GHQ-30	Dementia diagnosis; DSM-IV or medical records (n=90); OR 1.62 (0.59-4.41)
17 18 19	Petkus et al. 2016 (n=1082)	Prospective, community based cohort; Swedish twins drawn from Swedish Twin Registry, Sweden	Follow up period; 28 (0)	60.86 (11.15) – mean age at inclusion	612 (56.6)	Beyond elementary education; 423 (39)	29.8	MMSE	State anxiety subscale of STPI; STPI > 1 SD Q1-Q4 (assessments over 4 time-points)	403, 37%	Yes; OARS depression subscale, CES-D	Dementia diagnosis; DSM-III or DMS-IV (n=172); HR 1.48 (1.01-2.18)
20 21 22 23	Zilkens et al. 2014 (n=27136)	Population based matched case-controlled, Western Australia	Mean look back period; cases 20.4 (10.4), controls 20.0 (10.3)	78.7 (4.7) – mean age at final time point	15359 (56.6)	NR	6.17 (excluded individuals)	NR	Clinical diagnosis using ICD-10 AM (Australian Modification) codes documented in health records; meeting diagnostic threshold	379, 2.8% cases	Yes; clinical diagnosis by GP	Dementia diagnosis; ICD-10 (n=13568); OR 1.61 (1.28-2.02) (>10 years look back period)

(CES-D = Centre of Epidemiological Studies depression subscale, DLB = Dementia with Lewy bodies, GHQ-30 = 30-item general health questionnaire, NR = not recorded; OARS = older American resources and services; STAI = State trait anxiety inventory; STPI = State trait personality inventory)

Table 2 Case controlled studies: Newcastle-Ottawa scale for assessment of quality of included case controlled studies (+ / - represents whether individual criterion within the subsection was fulfilled)

	Acceptable Criteria	Zilkens et al. 2014		Boot et al. 2013	
Selection					
Case definition	With independent validation	Record linkage from Western Australian Data Linkage System and Death Registry, no independent validation	-	Assessment for DLB using behavioural neurologist	+
Representativeness of cases	Consecutive or representative series of cases	All dementia cases in period 2000-2009 identified via read-code; lower limit index dementia age 65 years, upper limit 84 years; dementia in other diseases excluded	+	Recruited from longitudinal studies in period 1984-2013 (Alzheimer Disease Patient Registry, Alzheimer Disease Research Centre Study, and Mayo Clinic Study of Ageing); community dwelling persons aged 70-89 years; excluded structural brain lesions	+
Selection of controls	Community controls	Population controls; randomly selected from electoral role aged ≥65 years prior to extraction of health data for controls	+	Community controls from longitudinal study of ageing; individuals aged ≥65 years; selected if seen by physician in same month as clinical subject diagnosed; matched by age and sex	+
Definition of controls	No history of disease	Excluded if dementia read-code in records; no independent screening	+	Excluded if diagnosed with DLB/AD during the study, previous stroke, head injury, neurologic disease or movement disorder; extensive cognitive and medical examination	+
Comparability					
Comparability of cases and controls on basis of design and analysis	Study controls for the most important factor (+/-), and any additional factor (+/-)	Controls for age, sex, vascular risk factors (diabetes, IHD, AF, CVD, hypertension, hyperlipidaemia, heart failure and past or current smoking), head injury, alcohol dependence syndrome, and depression	+	Controls for age, sex; multivariate analyses control for family history, depression, APOE ε4 alleles, education level, head injury, cancer, and vascular risk factors (stroke, diabetes, alcohol, smoking)	+
Exposure					
Ascertainment of exposure	Secure record, structured interview by healthcare practitioner	Secure administrative health record, read-codes for mid-life factors documented between aged 30-65 years within years 1966-2009	+	Anxiety history from medical history section of medical record	+
Same method of ascertainment for cases and controls	Yes	Yes; review of risk factor read-codes	+	Yes; review of medical history	+
Non-response rate	Similar for both cases and controls	NR	-	NR	-
Total Score			7		8

(DLB = Dementia with Lewy bodies; NR = not recorded)

Table 3 Cohort studies: Newcastle-Ottawa scale for assessment of quality of included cohort studies
(+ / - represents whether individual criterion within the subsection was fulfilled)

	Acceptable Criteria	Petkus et al. 2016		Gallacher et al. 2009	
Selection					
Representativeness of exposed cohort	Representative of average adult in the community (age/sex)	Population based Swedish twin registry, subsample of twins aged ≥ 50 years	+	Men only, representative of male inhabitants of Caerphilly region	-
Selection of non-exposed cohort	Drawn from same community as exposed cohort	Drawn from same community as exposed cohort	+	Drawn from same community as exposed cohort	+
Ascertainment of exposure	Secured records, clinical diagnosis using diagnostic tools (ICD-10/DSM-V)	State anxiety subscale of the State-Trait Personality Inventory (STPI), containing a subset of items from the STAI	+	Structured interview using STAI	+
Demonstration that outcome of interest was not present at start of study	Assessment for dementia at initial enrolment	No baseline screening, exclusion if previous dementia diagnosis, age at inclusion (mean age 60.86 years) makes cognitive impairment unlikely	-	Age at inclusion (mean age 56.1 years) makes cognitive impairment unlikely	-
Comparability					
Comparability of cohorts on basis of design or analysis	Study controls for the most important factor (+), and for any additional factor (+)	Multivariate models control for depression symptoms, baseline age, sex, education, physical illness	+	Study controls for age, social class, marital status, vascular risk factors (alcohol consumption, BP, BMI, total cholesterol, previous vascular disease), educational ability (National Adult Reading Test), and depression symptoms (GHQ-30)	+
Exposure					
Assessment of outcome	Independent blind assessment, record linkage	Screening for dementia using MMSE, cognitive in-person testing (assessing a range of cognitive domains), DSM-III or IV, and record linkage using National Patient Registry and National Patient Cause of Death Registry	+	Cognitive function assessed using CAMDEX, FAB, CDR; diagnosis made using DSM-IV, screening of primary care and hospital records	+
Follow up adequate for outcome to occur	Follow up >10 years	28 years	+	>20 years	+
Adequacy of follow up of cohorts	Complete follow up, or subjects lost to follow-up unlikely to introduce bias	NR	-	20% lost to follow up	+
Total Score			7		7

(BMI = body mass index; BP = blood pressure; CAMDEX = Cambridge mental disorders of the elderly examination; CDR = clinical dementia rating; DSM III/IV/V = Diagnostic and statistical manual of mental disorders III/IV/V; FAB = frontal assessment battery; GHQ-30 = 30-item general health questionnaire; ICD-10 = International classification of diseases 10; MMSE = mini mental state examination; NR = not recorded; STAI = State trait anxiety inventory)

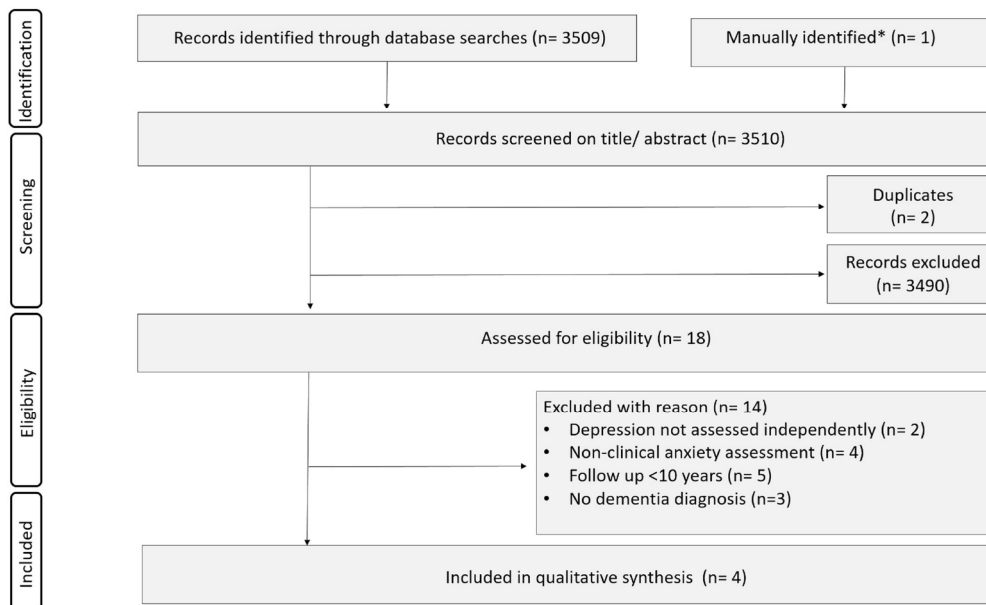


Figure 1 Flowchart of the search and study selection process; * = manually identified from Petkus et al. (2016)

175x106mm (300 x 300 DPI)

Example Search Strategy

Search carried out in Ovid MEDLINE(R) from 1946 to October Week 3 2017

#	Searches	Results
1	dement*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	101878
2	limit 1 to (english language and humans)	84635
3	alzheimer*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	123908
4	limit 3 to (english language and humans)	98174
5	mild cognitive impairment.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	10469
6	limit 5 to (english language and humans)	9789
7	MCI.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	12968
8	limit 7 to (english language and humans)	10517
9	2 OR 4 OR 6 OR 8	155363
10	anx*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	196896
11	limit 10 to (english language and humans)	154215
12	generalised anxiety disorder.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	475
13	limit 12 to (english language and humans)	438
14	GAD.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	7550
15	limit 14 to (english language and humans)	4299
16	11 OR 13 OR 15	156261
17	risk*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	2086806
18	limit 17 to (english language and humans)	1757965
19	odds.mp. [mp=ti, ot, ab, tx, kw, ct, sh, nm, hw, kf, px, rx, an, ui, eu, pm, sy, tc, id, tm, tn, dm, mf, dv, fs]	268449
20	limit 19 to (english language and humans)	257505
21	18 OR 20	1849508
22	9 AND 16 AND 21	776



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6,7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2, 9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7,17
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6,7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10,19,20
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10,19,20
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8,9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12,13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11,12,13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

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